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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/443,070 | 11/18/99 | GILTON | T 3530.2US |

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| EXAMINER | |
|---|---|
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| **ART UNIT** | **PAPER NUMBER** |
| 1641 | 9 |

**DATE MAILED:** 12/05/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/443,070 | GILTON, TERRY L. | |
| | Examiner | Art Unit | |
| | Gailene R. Gabel | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *27 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,8 and 12-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

## DETAILED ACTION

### *Amendment Entry*

1. Applicant's amendment and response filed 9/27/00 in Paper No. 7 is acknowledged and has been entered. Claims 3-7 and 9-11 have been cancelled without prejudice. Claims 1, 12-13, 20, 22, and 24-25 have been amended. Claims 1-2, 8, and 12-29 are pending and under examination.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. The rejection of claims 3-4 and 6-7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is now moot in light of Applicant's cancellation of the claims.

3. Claims 12-13 and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 has improper antecedent basis problem in reciting "**a** capillary column". See also claims 13, 24 and 25.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. The rejection of claims 3-5 and 9-11 under 35 U.S.C. 102(b) is now moot in light of Applicant's cancellation of the claims.

5. Claims 1-2, 8, 14-16, 18-20, 22-23, and 26-28 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Isaka et al. (US 5,482,598) for reasons of record.

6. In light of Applicant's argument, the rejection of claims 17 and 29 under 35 U.S.C. 102(e) as being clearly anticipated by Northrup et al. (US 5,882,496) is, hereby, withdrawn.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The rejection of claims 6 and 7 under 35 U.S.C. 103(a) as being unpatentable over Isaka et al. (US 5,482,598) in view of Yu (US 5,583,281), is now moot in light of Applicant's cancellation of the claims.

8. Claims 12-13, 21, and 24-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Isaka et al. (US 5,482,598) in view of Sunzeri (US 5,536,382) and Swedberg et al. (US 5,571,410) for reasons of record.

***New Grounds of Rejection***

9. Claims 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaka et al. (US 5,482,598) in view of Northrup et al. (US 5,882,496).

Isaka et al. disclose a method of separating a desired constituent from a sample (fluid), such as gas or liquid, efficiently without requiring a packing material on a chromatograph apparatus. Specifically, Isaka et al. disclose using a chromatography apparatus comprising a microchannel element with a matrix which extends across a semiconductor substrate (see column 1, lines 36-40 and column 2, lines 18-19). The semiconductor substrate comprises of silicon (see column 6, lines 5-7). The matrix is formed with a desired pattern, i.e. linear, circular, on the semiconductor substrate by incorporating a porosity thereon in order to create a porous portion with increased pore size and extended branching of the pores on the semiconductor surface (see Abstract and column 1, lines 35-46). Isaka et al. disclose applying the sample to a first end of

the matrix (injecting a mixture into an inlet port) then drawing the sample across a flowfront through the porous matrix channel from the second end (outlet port) by capillary action. The porous matrix functions as a filter which enhances separation of the desired constituent from the sample (see column 4, lines 16-27). The first end (inlet port) may also be coupled to a pump so that differential pressure can be applied to effect drawing a solution identified by the difference in flow rate between gases and liquids using a differential refractometer. Separation may involve a capture substrate (immobilized enzyme) wherein separation is on the basis of an affinity of the constituent with the capture substrate in a reaction (absorptivity involving immobilized enzyme) (see column 3, lines 1-14 and 50-54). Isaka et al. specifically teach application of the apparatus in solid-gas separation, solid-liquid separation, liquid-liquid separation, and gaseous separation, i.e. gas chromatography. The length of the matrix channel is not limited although its length is preferably larger than its diameter and the porosity of the matrix is preferably 10-90% (see column 2, lines 18-25 and lines 60-63). Isaka et al. further disclose separation of constituents on the basis of size by suggesting optimizing the pore size and pore shape of the matrix in accordance with the constituent being separated and measured, i.e. selecting the type and concentration of a dopant (see column 3, lines 35-42). Finally, Isaka et al. disclose using an ion column detector on the capillary for detecting presence of the constituent, i.e. absorption detector or fluorescence detector (see column 3, lines 16-24).

Isaka et al. differ in failing to teach applying an electrical current across the length of the capillary column.

Northrup et al. disclose isolation of constituents and filtering of components in a sample using porous silicon structures in miniaturized electrophoresis devices (see Abstract). In electrophoresis devices, electrodes within or adjacent a porous membrane (capillary column) can be used to draw sample across the flow front to control flow of electrically charged biochemical species (see column 5, lines 21-67). A negative electrode is formed at one end (inlet) of the porous silicon membrane (column) and a positive electrode is formed is formed at an opposite end (outlet) of the porous silicon membrane, thereby forming microelectrophoresis channels (see column 7, lines 38-50). Figure 3 illustrates porous silicon embodiment on a controlled flow interface device. Figure 8 illustrates a porous silicon electrophoresis device. Northrup et al. disclose that porous silicon particles have very small pore diameters so that they can be produced with relatively high degree of uniformity and control and because of its high surface area and specific pore size, porous silicon can be utilized for a variety of applications on a miniature scale for significantly augmenting adsorption, vaporization, desorption, condensation, and flow of liquids and gasses while maintaining the capability of modification such as being doped or coated using conventional integrated circuit and micromachining (see Summary).

One of ordinary skill in the art at the time of the instant invention would have reasonable expectation of success in substituting application of electrical current across

the length of a separation column such as taught by Northrup into the capillary column taught by Isaka in drawing a sample across the flowfront of the column because application of electrical current in separation devices to separate constituents from a sample (electrophoresis) is well known in the art. In addition, electrical current application in separation methods and devices constitutes an obvious design choice or modification of a mode of microfluidic transport which is routinely varied in the art and which has not been described as being critical to the practice of the invention.

***Response to Arguments***

10. Applicant's arguments filed 9/27/00 have been fully considered but they are not persuasive.

A) Applicant argues that Isaka does not anticipate the claimed invention because claim 1, as amended, recites a separation method that includes application of a sample to an end of a capillary column that includes at least one capture substrate disposed on the matrix of the porous capillary column to enhance separation of the constituent from the sample. Specifically, Applicant argues that the enzyme disclosed in Isaka is not a capture substrate, but rather, an enzyme that reacts and "detectably alters" the substrate whereas the capture substrate in the instant invention reacts by "capturing" the analyte without substantially altering the analyte. Applicant further argues that Isaka does not disclose binding and detecting the constituent with a stationary phase such as recited in claim 18 of the instant invention.

In response, Isaka indeed anticipates the instant claimed invention because the same basic elements and mechanism of "capturing, isolating, and detecting a constituent from a sample" is taught in Isaka wherein the porous matrix functions as a filter to enhance separation of the desired constituent from the sample (see column 4, lines 16-27) and wherein the porous matrix may include a capture substrate, in this case an **immobilized** enzyme, to effect separation based on the affinity of the constituent with the capture substrate. In column 3, lines 10-11, Isaka specifically discloses that "uricase is immobilized in the porous channel to check (by capturing and detecting) the amount of uric acid in serum" in the sample and does not require that the captured constituent in the matrix be necessarily altered- only that the captured constituent is isolated by immobilization into an affinity species in the matrix and then detected. Alternatively, the rejected claims do not exclude altering the constituent after binding to the capture substrate to effect detection of the constituent.

B) Applicant argues that Isaka does not disclose "detecting a constituent with at least one detector disposed proximate the detection region and contends that the enzymes in Isaka are not detectors.

Contrary to Applicant's argument, Isaka, indeed, disclose a column detector on the capillary matrix for detecting presence of a constituent, i.e. absorption detector or fluorescent detector in column 3, lines 16-24.

C) Applicant argues that Northrup does not anticipate the instant invention because both claims 17 and 29 depend from claims 1 and 18.

In response, see new ground of rejection in paragraph no. 9 and discussion thereafter.

D) Applicant argues that there is no motivation to combine the teachings of Sunzeri and Swedberg with Isaka because 1) the specific binding partner in Sunzeri is not immobilized to the capillary substrate, 2) Isaka fails to disclose and suggest that the "capture substrate" is useful in separation techniques, and 3) Swedberg teaches a method that includes forming an open trench in a substrate filled with different synthetic porous materials; therefore, one of ordinary skill in the art would not have been motivated to apply the teachings of Swedberg to the subject matter of Isaka. Moreover, Applicant argues that different types of matrix materials are used between Swedberg and Isaka references so that one of ordinary skill in the art would not have been motivated to combine both teachings.

Contrary to Applicant's contention, Isaka does disclose and suggest the usefulness of capture substrate in separation techniques in column 4, lines 16-27 wherein the porous matrix of the column functions as a filter which enhances separation of the desired constituent from the sample and wherein separation may involve a capture substrate (immobilized enzyme) to effect separation on the basis of affinity of

the constituent with the capture substrate in a reaction (see column 3, lines 1-14 and 50-54).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the rejection is based on the combined teachings of the references as follows. Isaka discloses a method of isolating constituents in a sample, such as gas or liquid using a chromatography apparatus wherein the sample is applied to a first end of the capillary matrix then drawn across a flowfront through the porous matrix channel from the second end by capillary action or, otherwise, by differential pressure. The porous matrix functions as a filter which enhances separation of the desired constituent from the sample and may include a capture substrate (immobilized enzyme) wherein separation is on the basis of affinity or absorptivity of the constituent with the capture substrate in a reaction. Sunzeri is incorporated only for his teaching of the benefit of including internal and external standards or controls alongside sample analysis in capillary electropheresis. Swedberg is incorporated for his teaching of a stationary phase in miniaturized column devices onto which separation and capture functions are combined in a particular matrix such as in an affinity chromatography matrix which specifically includes a variation of selected biological affiants: an antibody, an antigen, a

lectin, enzyme etc. to function as the capture species (see column 27, lines 43-61 and Example 1).

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Therefore, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the capture substrate in the chromatographic separation apparatus taught by Isaka to include other capture species such as antigens and antibodies, such as taught in the affinity chromatographic matrix of Swedberg in order to achieve enhanced simultaneous performance of separation, filtration, and capture function in a single chromatographic device because Swedberg specifically suggested that a variation of capture species can be incorporated into separation devices to

perform such capture function. One of ordinary skill in the art would have been motivated to combine the teachings of Swedberg in incorporating a variation of species into a separation matrix with teaching of Isaka in using porous silicon matrix in a capillary column for separation because Isaka specifically taught the advantage of porous silicon as matrix because of its established porosity which enhances capacity for separation, augments adsorption, differentiates flow rate in samples, thereby producing a highly versatile miniaturized chromatographic device capable of enhanced partitioning and complexation reactions. Furthermore, with the advent of silicon micromachining and LIGA in the teachings of Swedberg, one of ordinary skill in the art would have reasonable expectation of success in fabricating multiple separation columns or channels with a high degree of uniformity and precision in order to allow side by side accurate comparative and correlative measurement of sample results in comparison to internal controls, references, or standards with known measurement levels such as taught by Sunzeri, because quality control monitoring is standard laboratory practice and a well known art for monitoring the functionality, accuracy, and precision of various laboratory apparati and methods.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00

AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

11/29/01

Gailene R. Gabel
Patent Examiner
Art Unit 1641

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641